27227-445

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 30 1995

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Acute Mammalian Toxicity Data in Support of Registration of Methoprene End-Use Product, Altosid Pellets, by Sandoz Agro, Inc. (ID # 002724-00448; Barcode D206771; Submission # S472104; Chemical Code Number 105401; Case No. 010616)

TO: Willie H. Nelson
Regulatory Action Leader
Biopesticides and Pollution Prevention Division (7501W)

FROM: Sheryl K. Reilly, Ph.D., Biologist SKR
Biopesticides and Pollution Prevention Division (7501W)

THRU: J. Thomas McClintock, Ph.D., Team Leader JTMc
Biopesticides and Pollution Prevention Division (7501W)

ACTION REQUESTED: Review of six acute mammalian toxicity data in support of the registration of Altosid Pellets.

CONCLUSIONS: The studies are summarized as follows:

MRID NO.: 433338-01 Acute Oral Toxicity – Rat (152-10)
Sprague-Dawley rats (10/sex) were treated with a single oral dose of Altosid Pellets and observed for 14 days following dosing. Altosid Pellets was prepared for administration by grinding with a mortar and pestle and mixing with distilled water to provide a 500 mg/mL solution. Rats were treated with the 500 mg/mL solution of Altosid Pellets at 10.2 mL/kg (5100 mg/kg) body weight. There were no deaths during the study. Body weights increased for all males over the 14 day observation period. However, 1 female lost weight and 2/5 had no weight gain from days 8 to 15. There were no significant clinical signs during the study, and no significant pathological observations at termination. The oral LD_{50} for Altosid Pellets is > 5100 mg/kg body weight for Sprague-Dawley rats. The study is acceptable, and places the test material in **Toxicity Category IV.**

MRID NO.: 433338-02 Acute Dermal Toxicity - Rabbit (152-11)
Six male and five female Hra:(NZW)SPF rabbits were treated with a single dermal dose of Altosid Pellets at 2100 mg/kg body weight for 24 hours and observed for 14 days following treatment. For treatment, Altosid Pellets was ground with a mortar and pestle, added to gauze, and moistened with saline. There was no mortality, severe dermal irritation, adverse clinical signs, and no significant macroscopic pathological findings in the study. Therefore, under the conditions of this study, the dermal LD_{50} for Altosid Pellets is greater than 2100 mg/kg body weight for New Zealand White rabbits. This places Altosid Pellets in **Toxicity Category III**. This study is acceptable.

MRID NO.: 433338-04 Primary Eye Irritation – Rabbit (152-13)
Hra:(NZW)SPF rabbits (4 males, 5 females) were treated with a single ocular dose (0.1 cm^3/eye) of ground, dry Altosid Pellets. The test material was administered into the lower conjunctival sac of the right eye of each animal and the eye held shut for 1 second. The eyes of 3 animals (2 males, 1 female) were washed with lukewarm water 20-30 seconds after dosing. The eyes of the other rabbits and 2/3 rabbits in the washed eyes group were washed 24 hours after dosing to remove remaining residual test material. The left eye of each rabbit served as a control. The eyes of all rabbits were checked for irritation at 1, 24, 48, and 72 hours, 6 and 7 days after dosing or until irritation cleared. Eye irritation for rabbits in the unwashed eyes group at 1 hour post-treatment consisted of mild to severe conjunctivitis and slight iritis, progressing to mild to severe conjunctivitis, slight to moderate iritis, and mild corneal opacity and mild to moderate ulceration at 24 and 48 hours post-treatment. At 72 hours post-treatment, eye irritation consisted of mild or moderate redness and mild chemosis, with no iritis or corneal effects. There was no eye irritation noted at day 7 post-treatment. In the washed eye group, eye irritation consisted of mild to moderate conjunctivitis and slight iritis at 1 hour and mild conjunctivitis at 24 hours post-treatment. Ocular irritation was no longer present in 3/3 rabbits in the washed eye group by 48 hours post-treatment.

Under the conditions of the study, Altosid Pellets are mildly irritating to the eyes of New Zealand White rabbits and the test compound is placed in **Toxicity Category III.** This study is acceptable.

MRID NO.: 433338-05 Primary Dermal Irritation – Rabbit (152-14)
New Zealand white (Hra:(NZW)SPF) rabbits (3 males, 3 females) were treated with a single dermal dose (0.5 g) of Altosid Pellets. The test material was ground, moistened with saline, applied to the shaved backs of the rabbits, covered with gauze, and was removed by wiping 4 hours later. Rabbits were observed at 0.5, 24, 48, and 72 hours after removal of wrapping. There was no erythema and no edema noted in 6/6 rabbits at any timepoint after removal of the wrappings. The primary irritation index was 0.0. There were no clinical signs of toxicity, and no mortality.

As there were no signs of skin irritation at any timepoint after exposure, including 72 hours, **Altosid Pellets is not an irritant** to the skin of New Zealand white rabbits and is placed in **Toxicity Category IV.** This study is **Acceptable**.

MRID NO.: 433338-06 Dermal Sensitization, Buehler Method – Guinea Pig (152-15)

Dunkin Hartley albino (Haz:(DH)fBR) guinea pigs (10/sex) were treated with 0.3 cm^3 (moistened with 0.3 mL saline) Altosid Pellets for 6 hours, once per week for 3 weeks. Two weeks after the third exposure, the guinea pigs were challenged with test material applied to a naive skin site. In order to distinguish an irritation reaction from sensitization, an irritation control group (5/sex) of guinea pigs were subjected to the challenge procedure only. A positive control group (5/sex) was subjected to induction with 0.3 mL of 0.005 g/mL dinitrochlorobenzene (DNCB) and to challenge with 0.3 mL of 0.003 g/mL DNCB. An irritation control for DNCB was treated similarly with a challenge dose, but without the induction series. There were no dermal responses to Altosid Pellets after the first induction dose. Dermal responses after challenge with Altosid Pellets consisted of very slight (score = 0.5) erythema at 24 hours in 1 female, and no responses in any of the guinea pigs at 48 hours post-exposure. There was no mortality and no treatment-related effects on body weight gain for males or females. There were no clinical signs of toxicity reported.

Under the conditions of the study, Altosid Pellets did not cause contact sensitization in Dunkin Hartley guinea pigs. This study is **Acceptable**.

The Data Evaluation Reports are attached.

EPA Reviewer: Sheryl Reilly, Ph.D. SLR Date: 8/29/95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity – Rat (152-10)

CASE NO: 010616

TOX. CHEM. NO: 105401

DP BARCODE: 206771

MRID NO.: 433338-01

TEST MATERIAL: Altosid Pellets

SYNONYMS: Methoprene

STUDY NUMBER: Pharmaco LSR Study Number: 93-0856; Zoecon Study Number: 2032

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers Road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Acute Oral Toxicity Study of Altosid Pellets in Rats

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: February 25, 1994 (study completion date)

EXECUTIVE SUMMARY: Sprague-Dawley rats (10/sex) were treated with a single oral dose of Altosid Pellets and observed for 14 days following dosing. Altosid Pellets was prepared for administration by grinding with a mortar and pestle and mixing with distilled water to provide a 500 mg/mL solution. Rats were treated with the 500 mg/mL solution of Altosid Pellets at 10.2 mL/kg (5100 mg/kg) body weight.

There were no deaths during the study. Body weights increased for all males over the 14 day observation period. However, 1 female lost weight and 2/5 had no weight gain from days 8 to 15. There were no significant clinical signs during the study, and no significant macroscopic pathological observations at termination.

The oral LD_{50} for Altosid Pellets is greater than 5100 mg/kg body weight for Sprague-Dawley rats. This study is **Acceptable**, and Altosid Pellets are classified in **Toxicity Category IV.**

A. MATERIALS

1. Test material: Altosid Pellets

   Description: dark gray to black pellets with a slight hydrocarbon odor
   Lot/Batch No.: 93040101
   Purity: responsibility of the sponsor
   Stability of compound: responsibility of the sponsor

2. Test animals

   Species: rat
   Strain: Sprague-Dawley CD
   Age and weight at study initiation: 9-12 weeks; Pretest (day 0): 305-327 g (males), 217-235 g (females)
   Source: Charles River Breeding Laboratories, Inc., Kingston, New York 12484

3. Animal care

   Housing: individually in suspended, stainless steel cages with wire mesh bottoms
   Food: Certified Purina Rodent Diet No. 5002 (Meal), Purina Mills, Inc., St. Louis, MO, *ad libitum*
   Water: municipal water supply, automatic watering system, *ad libitum*
   Acclimation period: 9 days
   Environmental conditions:
      Temperature: 68-76°F
      Humidity: 52-70%
      Photoperiod: 12 hour light/dark cycle

B. METHODS

After a 20 hour fast, 10 rats (5/sex) were given a single oral dose (5100 mg/kg body weight) administered with a ball-tipped intubation needle fitted to a syringe. The test material was prepared for administration by grinding Altosid Pellets with a mortar and pestle, adding distilled water and mixing with a homogenizer to produce a 500 mg/mL mixture. The test material was prepared a few hours prior to dosing and was again mixed well immediately prior to dosing. The individual doses were determined based upon day 0 (prior to fasting) body weights. Animals were observed at 1, 2, and 4 hours after administration of test material and once daily thereafter for 14 days for general condition, and abnormalities of skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as evaluations of respiration and palpation for tissue masses. Animals were observed twice daily for mortality. Food consumption was not monitored. Body weights were recorded at day 0 (prior to fasting), day 1 (just prior to dosing), and days 8 and 15 (termination). At termination, all surviving animals were euthanized by carbon dioxide inhalation and gross necropsies performed. The macroscopic pathological examination included the external surface, all orifices, the organs and tissues of the cranial, thoracic, abdominal, and pelvic cavities, the neck and the remainder of the carcass. The LD_{50} was not calculated using a statistical method as there was no mortality.

C. RESULTS

1. Mortality

There were no deaths during the study. The LD_{50} is greater than 5100 mg/kg for males and females.

2. Clinical observations

There were no pharmacologic and toxicological abnormalities noted.

3. Body weight

Body weight increases from day 0 to day 8, ranged from 43-57 g for males, and from 12-38 g for females. Body weight increases from day 0 to day 15, ranged from 51-80 g for males, and from 24-44 g for females (mean body weight gains were 65.6 g for males and 33.0 g for females). Body weights increased from day 8 to 15 for 5/5 males and 2/5 females. Body weights decreased for 1 female (9 g decrease) and 2 females had weight gains of 0 g from day 8 to 15.

4. Necropsy

There were no significant macroscopic pathological observations.

5. LD_{50}

Under the conditions of this study, the oral LD_{50} for Altosid Pellets is greater than 5100 mg/kg body weight for Sprague-Dawley rats. Altosid Pellets are classified in Toxicity Category IV.

D. Signed and dated Quality Assurance and GLP statements were present.

E. STUDY DEFICIENCIES

The study report (MRID No. 433338-01), p. 13, contains a portion of the Methods section for a dermal study. These methods do not apply to an oral study. It is assumed by the reviewer that these statements were inadvertently included in the report, and that the paragraphs that should have been included do not contain information that would change the conclusions of the study report.

DATA EVALUATION REPORT

ALTOSID PELLETS

Study Type: ACUTE GAVAGE – RAT (81-1)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
C. Scott Jamison, Ph.D.
Signature: C. S. Jamison
Date: 8/8/95

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T.
Signature: C B Bast
Date: 8-23-95

Robert H. Ross, M.S., Group Leader
Signature: R H R
Date: 8-23-95

Quality Assurance:
Susan Chang, M.S.
Signature: S Chang
Date: 8/22/95

Disclaimer

The final Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EPA Reviewer: Sheryl Reilly, Ph.D. 5142 Date: 8/29/95
Biopesticides and Pollution Prevention Division

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity - Rabbit (152-11)

CASE NO: 010616

TOX. CHEM. NO: 105401

DP BARCODE.: D206771

MRID NO.: 433338-02

TEST MATERIAL: Altosid Pellets

SYNONYMS: Methoprene

STUDY NUMBER: Pharmaco LSR Study No.: 93-0857; Zoecon Study Number: 2033.

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Acute Dermal Toxicity Study of Altosid Pellets in Rabbits

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: February 25, 1994 (study completion date)

EXECUTIVE SUMMARY: Six male and five female Hra:(NZW)SPF rabbits were treated with a single dermal dose of Altosid Pellets at 2100 mg/kg body weight for 24 hours and observed for 14 days following treatment. For treatment, Altosid Pellets was ground with a mortar and pestle, added to gauze, and moistened with saline.

There was no mortality, severe dermal irritation, adverse clinical signs, and no significant macroscopic pathological findings in the study. Therefore, under the conditions of this study, **the dermal LD_{50} for Altosid Pellets is greater than 2100 mg/kg body weight for New Zealand White rabbits.** This places Altosid Pellets in **Toxicity Category III**. This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid Pellets

   Description: dark gray to black pellets with a slight hydrocarbon odor
   Lot/Batch No.: 93040101
   Purity: responsibility of the sponsor
   Stability of compound: responsibility of the sponsor
   Active ingredient: not reported

2. Test animals

   Species: rabbit
   Strain: New Zealand White, Hra:(NZW)SPF
   Age and weight at study initiation: ≥8 weeks, 1.9-2.2 kg (males), 2.0-2.3 kg (females)
   Source: HRP, Inc., Denver, PA

3. Animal care

   Housing: individually in suspended, stainless steel cages with wire mesh bottoms
   Food: Lab Rabbit Chow HF (Purina #5326)
   Water: municipal water supply, automatic watering system, *ad libitum*
   Acclimation period: 15 days for 6 males, 4 females; 30 days for 1 female
   Environmental conditions:
      Temperature: 62-73°F
      Humidity: 36-70%
      Photoperiod: 12 hour light/dark cycle

B. METHODS

All animals had body weights within 20% of the mean for each sex, and were considered suitable for use in the study based upon pretest physical examiniations. The hair on the dorsal surface and sides from the scapula to the pelvic area on each of six male and five female NZW rabbits was clipped with electric clippers 24 hours prior to dosing. At least 10% of the total body surface on each animal (12 cm x 14 cm) was exposed and no abrasions were noted. Altosid Pellets were prepared for administration by grinding with a mortar and pestle. The dry test material (2100 mg/kg body weight) was placed onto a 4 inch x 12 inch strip of 8-ply gauze and moistened with 1 mL of saline. The gauze was wrapped around the trunk of the animal, covering the application site. An impervious plastic sleeve was wrapped over the gauze and secured with Elastoplast tape, in order to contain the test material without leakage or undue pressure. Elizabethan collars were placed on all animals in order to prevent ingestion of the test material or disruption of the wrappings.

The bandaging was removed after 24 hours, and the test site wiped free of excess test material with distilled water and gauze. Animals were observed for signs of toxicity at 1, 2, and 4 hours after test material application and daily thereafter for 14 days for severe

dermal effects, general condition, and for abnormalities of skin and fur, eyes, nose, oral cavity, abdomen and external genitalia as well as evaluations of respiration and palpation for tissue masses. Mortality observations were performed twice daily. Body weights were determined at days 0 (prior to clipping), 1 (prior to dosing), 8, and 15 (termination). Day 0 body weights were used to calculate the doses. All animals were euthanitized at day 15 by an intravenous overdose of sodium pentobarbital and subjected to gross pathological examination of the external surface, all orifices, the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck and the remainder of the carcass. Food consumption data was not reported.

The LD_{50} was not calculated using statistical analysis as there was no mortality. The dermal exposures to Altosid Pellets at 2100 mg/kg corresponded to 25.6 mg/cm^2 for males and 26.75 mg/cm^2 for females (calculated by the reviewer). One female was found to be a male on gross pathological examination. Another female was then subjected to treatment with Altosid Pellets as described approximately 1 month after necropsy of the initial test group.

C. RESULTS

1. Mortality

There was no mortality during the 14-day observation period.

2. Clinical Observations

There were no treatment-related clinical signs.

3. Body Weight

Body weight gains ranged from -0.2 to 0.2 kg for males and for females.

4. Necropsy

The gross pathological findings consisted of mild discoloration, mild enlargement, severed dilatation, and abnormal contents (moderate) of the kidney of 1 male. These findings are not toxicologically significant. There were no gross pathological findings for the other males (5/6) or for the females (5/5) treated dermally with Altosid Pellets.

5. LD_{50}

The dermal LD_{50} for Altosid Pellets is greater than 2100 mg/kg body weight for New Zealand White rabbits. Based upon the LD_{50}, Altosid Pellets is classified in Toxicity Category III. This study is classified as Acceptable.

D. Signed and dated Quality Assurance and GLP statements were present.

DATA EVALUATION REPORT

ALTOSID PELLETS

Study Type: ACUTE DERMAL – RABBIT (81-2)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
C. Scott Jamison, Ph.D.

Signature: C. S. Jamison
Date: 8/8/95

Secondary Reviewers:
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Signature: CBBast
Date: 8-23-95

Robert H. Ross, M.S., Group Leader

Signature: RHR
Date: 8-23-95

Quality Assurance:
Susan Chang, M.S.

Signature: S S Chang
Date: 8/22/95

Disclaimer

The final Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EPA Reviewer: Sheryl Reilly, Ph.D. SLR Date: 8/29/95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation-Rabbit (152-13)

CASE NO: 010616

TOX. CHEM. NO: 105401

DP BARCODE.: D206771

MRID NO.: 433338-03

TEST MATERIAL: Altosid Pellets

SYNONYMS: Methoprene

STUDY NUMBER: Pharmaco LSR Study No.: 93-0859; Zoecon Study Number: 2035

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Primary Eye Irritation Study of Altosid Pellets in Rabbits

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: February 25, 1994 (study completion date)

EXECUTIVE SUMMARY: Hra:(NZW)SPF rabbits (4 males, 5 females) were treated with a single ocular dose (0.1 cm^3/eye) of ground, dry Altosid Pellets. The test material was administered into the lower conjunctival sac of the right eye of each animal and the eye held shut for 1 second. The eyes of three rabbits (2 males, 1 female) were washed with lukewarm water 20-30 seconds after dosing. The treated eyes of 6/6 rabbits in the unwashed eyes group and 2/3 rabbits in the washed eyes group were washed 24 hours after dosing to remove remaining residual test material. The left eye of each rabbit served as a control. The eyes of all rabbits were checked for irritation at 1, 24, 48, and 72 hours, 6 and 7 days after dosing or until irritation cleared.

Eye irritation for rabbits in the unwashed eyes group at 1 hour post-treatment consisted of mild to severe conjunctivitis and slight iritis, progressing to mild to severe conjunctivitis, slight to moderate iritis, and mild corneal opacity and mild to moderate ulceration at 24 and 48 hours post-treatment. At 72 hours post-treatment, eye irritation consisted of conjunctivitis (mild (3/6) or moderate (1/6) redness and mild (2/6) chemosis), with no iritis

or corneal effects. There was no eye irritation noted at day 7 post-treatment for 6/6 rabbits. In the washed eye group, eye irritation consisted of mild to moderate conjunctivitis and slight iritis at 1 hour and mild conjunctivitis at 24 hours post-treatment. Ocular irritation was no longer present in 3/3 rabbits in the washed eye group by 48 hours post-treatment.

As there were corneal effects (opacity and ulceration) at 24 and 48 hours post-treatment and because conjunctivitis was present at 1, 24, 48, and 72 hours, and 6 days post-treatment, but the irritation cleared within 7 days, **Altosid Pellets is classified as a mild irritant** to the eyes of male and female New Zealand White rabbits and is placed in **Toxicity Category III.** This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid Pellets

   Description: dark gray to black pellets with a slight hydrocarbon odor
   Lot/Batch No.: 93040101
   Purity: responsibility of the sponsor
   Stability of compound: responsibility of the sponsor
   Active ingredient: not reported
   *p*H: not reported

2. Test animals

   Species: rabbit
   Strain: New Zealand White, Hra:(NZW)SPF
   Age and weight at study initiation: ≥8 weeks; 2.0-2.4 kg
   Source: HRP, Inc., Denver, PA

3. Animal care

   Housing: individually in suspended stainless steel cages with wire mesh bottoms
   Food: Lab Rabbit Chow HF (Purina No. 5326)
   Water: municipal water supply, automatic watering system, *ad libitum*
   Acclimation period: 15 days
   Environmental conditions:
   Temperature: 63-70°F
   Humidity: 44-74%
   Photoperiod: 12 hour light/dark cycle

B. METHODS

Each rabbit (5 males, 4 females) was treated with a single dose (0.1 cm^3) of Altosid Pellets. which were ground with a mortar and pestle prior to administration. Both eyes of each animal were examined on the day before dosing using fluorescein dye to check for corneal ulceration and on the day of dosing (without dye). Only animals negative for corneal ulceration, conjunctival injury, or irritation were used in the study. The test material was introduced into the lower conjunctival sac of the right eye of each animal and the eyelids

held shut for 1 second to prevent loss of material. The left eye served as a control. After 20-30 seconds, the eyes of 3 rabbits (2 males, 1 female) were washed for approximately 1 minute with lukewarm water. The eyes of the remaining six rabbits (3 males, 3 females) were left unwashed. After 24 hours, the eyes of all 8/9 animals were rinsed to remove residual test material.

The eyes of all animals were examined at approximately 1, 24, 48, and 72 hours, 6 and 7 days after treatment. At each timepoint, treated eyes were examined and scored for ocular reactions in comparison to the untreated eyes. Ocular reactions were scored for the conjunctivae (redness, chemosis, discharge, and white tissue or ulceration), the iris, and the cornea (opacity, area of corneal involvement, stippling, and ulceration). Fluorescein dye was used to confirm the presence or absence of corneal ulceration, starting at the 24 hour examination. Eye examinations with fluorescein dye continued until there was no dye retention for 2 observations. Irritation was defined as the production of reversible changes. Eye corrosion was defined as the production of irreversible tissue damage to the eye following test material administration. Observations for mortality or clinical signs of toxicity were performed twice daily. There were no body weight changes reported by the study authors. At the termination of the study, all rabbits were euthanitized with sodium pentobarbital. There was no macroscopic examination of tissues.

C. RESULTS

The incidence of eye irritation is presented in Table 1, below. There was conjunctivitis present in males and females in the unwashed eyes group at 1, 24, 48, and 72 hours, and 6 days post-treatment, iritis present at 1 and 24 hours post-treatment, and corneal effects consisting of slight or mild opacity and mild or moderate ulceration at 1, 24, and 48 hours post-treatment. All irritation cleared by 7 days post-treatment.

For the washed eye group (2 males, 1 female), irritation consisted of mild to moderate conjunctivitis and slight iritis, at 1 hour post-treatment, and mild redness (2/3) at 24 hours post-treatment. There was no eye irritation observed at 48 or 72 hours post-treatment. Residual test material was present in the eyes of 3/3 rabbits at 1 hour, 2/3 rabbits at 24 hours, and 1/3 rabbits at 48 hours post-treatment, indicating that the 1 minute wash after administration of the test material was insufficient to remove the material from the eye. However, the severity of the irritation was reduced by the washing procedure.

The maximum mean irritation score (14.5) was obtained for rabbits in the unwashed eyes group at 24 hours post-treatment. Altosid Pellets is classified as a mild eye irritant in New Zealand white rabbits and is in Toxicity Category III.

D. Signed and dated Quality Assurance and GLP statements were present.

TABLE 1. INCIDENCE OF OCULAR IRRITATION IN MALE AND FEMALE NEW ZEALAND WHITE RABBITS TREATED WITH ALTOSID PELLETS

held shut for 1 second to prevent loss of material. The left eye served as a control. After 20-30 seconds, the eyes of 3 rabbits (2 males, 1 female) were washed for approximately 1 minute with lukewarm water. The eyes of the remaining six rabbits (3 males, 3 females) were left unwashed. After 24 hours, the eyes of all 8/9 animals were rinsed to remove residual test material.

The eyes of all animals were examined at approximately 1, 24, 48, and 72 hours, 6 and 7 days after treatment. At each timepoint, treated eyes were examined and scored for ocular reactions in comparison to the untreated eyes. Ocular reactions were scored for the conjunctivae (redness, chemosis, discharge, and white tissue or ulceration), the iris, and the cornea (opacity, area of corneal involvement, stippling, and ulceration). Fluorescein dye was used to confirm the presence or absence of corneal ulceration, starting at the 24 hour examination. Eye examinations with fluorescein dye continued until there was no dye retention for 2 observations. Irritation was defined as the production of reversible changes. Eye corrosion was defined as the production of irreversible tissue damage to the eye following test material administration. Observations for mortality or clinical signs of toxicity were performed twice daily. There were no body weight changes reported by the study authors. At the termination of the study, all rabbits were euthanitized with sodium pentobarbital. There was no macroscopic examination of tissues.

C. RESULTS

The incidence of eye irritation is presented in Table 1, below. There was conjunctivitis present in males and females in the unwashed eyes group at 1, 24, 48, and 72 hours, and 6 days post-treatment, iritis present at 1 and 24 hours post-treatment, and corneal effects consisting of slight or mild opacity and mild or moderate ulceration at 1, 24, and 48 hours post-treatment. All irritation cleared by 7 days post-treatment.

For the washed eye group (2 males, 1 female), irritation consisted of mild to moderate conjunctivitis and slight iritis, at 1 hour post-treatment, and mild redness (2/3) at 24 hours post-treatment. There was no eye irritation observed at 48 or 72 hours post-treatment. Residual test material was present in the eyes of 3/3 rabbits at 1 hour, 2/3 rabbits at 24 hours, and 1/3 rabbits at 48 hours post-treatment, indicating that the 1 minute wash after administration of the test material was insufficient to remove the material from the eye. However, the severity of the irritation was reduced by the washing procedure.

The maximum mean irritation score (14.5) was obtained for rabbits in the unwashed eyes group at 24 hours post-treatment. Altosid Pellets is classified as a mild eye irritant in New Zealand white rabbits and is in Toxicity Category III.

D. Signed and dated Quality Assurance and GLP statements were present.

TABLE 1. INCIDENCE OF OCULAR IRRITATION IN MALE AND FEMALE NEW ZEALAND WHITE RABBITS TREATED WITH ALTOSID PELLETS

Time Post-Treatment	Cornea		Iritis	Conjunctivitis			Mean Eye Irritation Score
	Opacity	Ulceration		Redness	Chemosis	Discharge	
Unwashed Eyes							
1 Hour	0/6	0/6	3/6	6/6	6/6	6/6	8.5
24 Hour	5/6	6/6	4/6	6/6	6/6	4/6	14.5
48 Hour	0/6	1/6	0/6	6/6	5/6	2/6	4.3
72 Hour	0/6	0/6	0/6	4/6	2/6	0/6	2.0
Day 6	0/2	0/2	0/2	1/2	0/2	0/6	1.0
Washed Eyes							
1 Hour	0/3	0/3	2/3	3/3	2/3	3/3	8.7
24 Hour	0/3	0/3	0/3	2/3	0/3	0/3	1.3
48 Hour	0/3	0/3	0/3	0/3	0/3	0/3	0.0
72 Hour	0/3	0/3	0/3	0/3	0/3	0/3	0.0

Data adapted from Tables I and II, pp. 21-25, MRID No. 433338-03.

DATA EVALUATION REPORT

ALTOSID PELLETS

Study Type: PRIMARY EYE IRRITATION – RABBIT (81-4)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
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Signature: C S Jamison
Date: 8/18/95

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Signature: C B Bast
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Robert H. Ross, M.S., Group Leader
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Date: 8-23-95

Quality Assurance:
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Signature: S S Chang
Date: 8/22/95

Disclaimer

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*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EPA Reviewer: Sheryl Reilly, PhD. SLR Date: 8/29/95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Primary Skin Irritation - Rabbit (152-14)

CASE NO: 010616

TOX. CHEM. NO: 105401

DP BARCODE.: D206771

MRID NO.: 433338-04

TEST MATERIAL: Altosid Pellets

SYNONYMS: Methoprene

STUDY NUMBER: Pharmaco LSR Study Number: 93-0858; Zoecon Study Number: 2034

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Primary Dermal Irritation Study of Altosid Pellets in Rabbits

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: February 25, 1994 (study completion date)

EXECUTIVE SUMMARY: New Zealand white (Hra:(NZW)SPF) rabbits (3 males, 3 females) were treated with a single dermal dose (0.5 g) of Altosid Pellets. The test material was ground, moistened with saline, applied to the shaved backs of the rabbits, covered with gauze, and was removed by wiping 4 hours later. Rabbits were observed at 0.5, 24, 48, and 72 hours after removal of wrapping.

There was no erythema and no edema noted in 6/6 rabbits at any timepoint after removal of the wrappings. The primary irritation index was 0.0. There were no clinical signs of toxicity, and no mortality.

As there were no signs of skin irritation at any timepoint after exposure, including 72 hours, **Altosid Pellets is not an irritant** to the skin of New Zealand white rabbits and is placed in **Toxicity Category IV.** This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid Pellets

   Description: dark gray to black pellets with a slight hydrocarbon odor
   Lot/Batch No.: 93040101
   Purity: responsibility of the sponsor
   Stability of compound: responsibility of the sponsor
   Active ingredient: not reported
   pH: not reported

2. Test animals

   Species: rabbit
   Strain: New Zealand White, Hra:(NZW)SPF
   Age and weight at study initiation: ≥ 8 weeks, 2.1-2.5 kg
   Source: HRP, Inc., Denver, PA

3. Animal care

   Housing: individually in suspended, stainless steel cages with wire mesh bottoms
   Food: Lab Rabbit Chow HF (Purina #5326)
   Water: municipal water supply, automatic watering system, *ad libitum*
   Acclimation period: 7 days
   Environmental conditions:
   Temperature: 66-70°F
   Humidity: 52-62%
   Photoperiod: 12 hour light/dark cycle

B. METHODS

Each of six rabbits (3/sex) was treated dermally for 4 hours with a single dose (0.5 g) of Altosid Pellets. Approximately 24 hours prior to application, the hair of each animal was clipped with an electric clipper to expose the back from the scapular to the lumbar region, and the skin was examined for abrasions (none were noted in any of the rabbits). The test material was ground with a mortar and pestle, and 0.5 g moistened with 0.5 mL of saline and applied directly to the backs of the rabbits. The test site was covered with gauze (1 inch x 1 inch, approximately 6 cm^2), held in place with tape. Gauze was then wrapped around each animal to hold the test material in place without undue pressure (semi-occlusive pressure). Elizabethan collars were used to restrain the animals during dosing to prevent disruption of the wrappings and ingestion of the test material. After 4 hours of exposure, wrappings were removed and the test site gently wiped free of excess material with gauze and distilled water. Dermal observations were made approximately 0.5, 24, 48, and 72 hours after removal of wrappings. The test site was examined for the presence of erythema, edema, or other evidence of dermal irritation, such as necrosis, eschar, other irreversible alteration of tissue structures, or other dermal abnormalities. Adjacent areas of untreated skin were used as controls. Any abnormal clinical signs of toxicity were noted. Mortality

checks were performed twice daily. At study termination, all rabbits were euthanized with an intravenous overdose of sodium pentobarbital. There was no gross necropsy performed.

C. RESULTS

For the rabbits (4 males, 2 females) treated dermally with Altosid Pellets, there was no erythema, edema, or other skin irritation evident at 0.5, 24, 48, or 72 hours after removal of wrappings. There were no clinical signs of toxicity reported. Body weight changes, if any, were not reported. No animals died during the study.

At 72 hours post-treatment, there was no skin irritation observable in males or females; thus, Altosid Pellets is placed in Toxicity Category IV.

D. Signed and dated Quality Assurance and GLP statements were present.

DATA EVALUATION REPORT

ALTOSID PELLETS

Study Type: PRIMARY SKIN IRRITATION – RABBIT (81-5)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
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Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
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Date: 8/8/95

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Robert H. Ross, M.S., Group Leader
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Quality Assurance:
Susan Chang, M.S.
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EPA Reviewer: Sheryl Reilly, Ph.D. SLR Date: 8/29/95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization, Buehler Method - Guinea Pig (152-15)

CASE NO: 010616

TOX. CHEM. NO: 105401

DP BARCODE.: D206771

MRID NO.: 433338-05

TEST MATERIAL: Altosid Pellets

SYNONYMS: Methoprene

STUDY NUMBER: Pharmaco LSR Study Number: 93-0860; Zoecon Study Number: 2036

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Closed Patch Repeated Insult Dermal Sensitization Study of Altosid Pellets in Guinea Pigs.

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: March 16, 1994 (study completion date)

EXECUTIVE SUMMARY: Dunkin Hartley albino (Haz:(DH)fBR) guinea pigs (10/sex) were treated with 0.3 cm^3 (moistened with 0.3 mL saline) Altosid Pellets for 6 hours, once per week for 3 weeks. Two weeks after the third exposure, the guinea pigs were challenged with test material applied to a naive skin site. In order to distinguish an irritation reaction from sensitization, an irritation control group of 5 male and 5 female guinea pigs were subjected to the same challenge procedures, but without the induction regimen. A positive control group (5/sex) was subjected to induction with 0.3 mL of 0.005 g/mL dinitrochlorobenzene (DNCB; dissolved in ethanol) and to challenge with 0.3 mL of 0.003 g/mL (dissolved in acetone) DNCB. An irritation control for DNCB was treated similarly with a challenge dose, but without the induction series.

All of the guinea pigs (10/10) treated dermally with DNCB exhibited appropriate skin irritation reactions after the first induction dose and after challenge. There were no dermal responses to Altosid Pellets after the first induction dose. Dermal responses after challenge

with Altosid Pellets consisted of very slight (score = 0.5) erythema at 24 hours in 1 female, and no responses in any of the guinea pigs at 48 hours post-exposure. For Altosid Pellets, the Incidence Index of Sensitization at 24 hours was 0% for the challenge and irritation control groups, and the Severity Indices at 24 hours and 48 hours were 0.025 and 0.0, respectively. There was no mortality and no treatment-related effects on body weight gain for males or females. There were no clinical signs of toxicity reported.

Under the conditions of the study, Altosid Pellets did not cause contact sensitization in Dunkin Hartley guinea pigs. This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid Pellets

Description: dark gray to black solid with a slight hydrocarbon odor
Lot/Batch No.: 93040101
Purity: responsibility of the sponsor
Stability of compound: responsibility of the sponsor
Active ingredient: not reported
pH: not reported
Density: not reported

2. Test animals

Species: guinea pigs
Strain: albino, Dunkin Hartley; Haz:(DH)fBR
Age and weight at study initiation: 5-6 weeks; 312-440 g (males), 318-435 g (females)
Source: HRP, Inc., Denver, PA

3. Animal care

Housing: individually in suspended, stainless steel cages with wire mesh bottoms
Food: Agway Prolab Guinea Pig Diet, *ad libitum*
Water: municipal water supply, automatic watering system, *ad libitum*
Acclimation period: 16 days
Environmental conditions:
Temperature: 64-75°F
Humidity: 30-80%
Photoperiod: 12 hour light/dark cycle

B. METHODS

1. Mortality, clinical signs, and body weights

Mortality checks were performed twice daily. Checks for general health were performed prior to treatment and once weekly and any abnormalities noted. Body weights were determined on the day prior to the first induction and at termination (2 days after challenge). Dermal responses were scored for erythema (scale: 0, no

reaction; 0.5, very slight; 1, slight; 2, moderate; 3, severe), edema, necrosis, and eschar.

2. Preliminary irritation study

An initial screening was performed in order to determine the irritancy of the test material. The hair was clipped short on the back and sides the guinea pigs on the day prior to the application of the test material. Altosid Pellets was ground with a mortar and pestle and applied topically to 6 guinea pigs at 100% (0.3 cm^3 in 0.3 mL saline), 50%, 25%, and 10% concentrations (w/v, diluted into distilled water). The test material mixtures were applied to each guinea pig beneath a Hilltop Chamber® in a volume of 0.3 mL. The chamber was occluded with overlapping, impermeable plastic and secured with an elastic adhesive bandage (Elastoplast®) wound around the torsos of the guinea pigs. The chambers were left in place for 6 hours, then removed and the skin wiped free of excess material with distilled water and gauze. Skin irritation observations were made at 24 and 48 hours.

3. Induction

Twenty guinea pigs (10 males, 10 females) were used for testing dermal sensitization of Altosid Pellets. Ten guinea pigs (5 males, 5 females) were used in the positive control group (DNCB). Altosid Pellets was ground with a mortar and pestle and 0.3 cm^3 moistened with 0.3 mL of saline. DNCB was dissolved in 80% ethanol to produce a 0.005 g/mL solution. The hair on the application site (back and sides) of was clipped short with an electric clipper on the day prior to each application. A Hilltop Chamber® was saturated with test material (0.3 cm^3 of Altosid Pellets in 0.3 mL saline or 0.3 mL of 0.005 g/mL DNCB). The test site was on the right side of the midline. The chamber was covered by overlapping impermeable plastic, held in place with Elastoplast® adhesive elastic bandage wound around the torso of the guinea pig. The chamber was left in place for 6 hours, then removed and the skin wiped free of excess material with distilled water and gauze. Induction was performed once a week, for 3 weeks. Dermal evaluations were made at 24 and 48 hours after the first induction exposure to confirm that a slightly irritating concentration of DNCB was used, and that an appropriate concentration of Altosid Pellets had been chosen.

4. Challenge

Fourteen days after the last induction exposure, the test material was administered at a site on the opposite side of the midline from the induction exposure test site. The method for the challenge exposure was the same as was used during the induction exposures, except that the dose of the positive control, DNCB, was lower (0.3 mL of 0.003 g/mL), and the solution used for dissolving DNCB was acetone, rather than ethanol. The dermal response was evaluated 24 and 48 hours after challenge treatment. The results were evaluated by the amount of erythema at the challenge site relative to irritation controls. Two indices were calculated to assess the dermal responses: incidence and severity. The incidence index is the number of animals with a response grade of ≥ 1 (at 24 or 48 hours) out of the total number of animals in the group. The severity index for the 24 and 48 hour response reading was determined by dividing the

sum total of the irritation grades in a group by the total number of animals exposed. At study termination, all guinea pigs were euthanitized by carbon dioxide inhalation. There was no gross necropsy performed.

C. RESULTS

1. Mortality, clinical signs, and body weights

There was no mortality. The guinea pigs were in good general health at each of the weekly observations. Body weights increased for males and females throughout the post-treatment observation period. Body weight gains for guinea pigs treated with Altosid Pellets ranged from 169-300 g for males, and from 131-219 g for females. These ranges of body weight gains were similar to those for the positive control (174-263 g for males, 123-186 g for females) and the negative/irritation control (187-292 g for males, 100-205 g for females).

2. Preliminary irritation study

The preliminary skin irritancy test results indicated that Altosid Pellets applied at 10%, 25%, or 50% was non-irritating to guinea pigs. For Altosid Pellets applied at 100%, very slight erythema was noted for 1 male at 24 hours, and there were no skin irritation reactions observed for 2/3 males and 3/3 females at either the 24 or 48 hour timepoints. There were no other clinical signs of toxicity reported. Altosid Pellets was used undiluted (100%) in the induction and challenge portions of the dermal sensitization test.

3. Induction

At the first induction with Altosid Pellets, there were no dermal responses for 20/20 guinea pigs at either 24 or 48 hours. All 10 guinea pigs treated with DNCB exhibited appropriate dermal responses at the first induction. Dermal responses for DNCB or for Altosid Pellets were only recorded by the study authors for the first induction exposure.

4. Challenge

Dermal responses for guinea pigs challenged with Altosid Pellets were not suggestive of an irritation or sensitization response. There was very slight erythema for 1 female at 24 hours after challenge. There were no dermal responses in 20/20 guinea pigs at 48 hours after challenge. The Incidence Index of Sensitization to Altosid Pellets at 24 hours was 0%. The Severity Indices at 24 and 48 hours were 0.025 and 0.0, respectively. For irritation controls treated with Altosid Pellets, there were no dermal responses in 10/10 guinea pigs. The Incidence Index of Sensitization at 24 hours was 0% for the irritation control group. The Severity Indices for the irritation control group were 0.0 and 0.0, at 24 and 48 hours, respectively. All 10 guinea pigs exhibited appropriate dermal responses to challenge with DNCB.

DATA EVALUATION REPORT

ALTOSID PELLETS

Study Type: DERMAL SENSITIZATION – GUINEA PIG (81-6)

Prepared for

Biopesticides and Pollution Prevention Division
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Task Order No. 95-1

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